

IN THE CLAIMS:

Claims 72-78 and 80-83 are pending in this application, wherein claims 72 and 73 have been amended, and claims 79 and 84-110 have been cancelled, as indicated below. This listing of claims will replace all prior versions, and listings of claims in the application.

1-71. (Cancelled)

72. (Currently Amended) A computer-implemented method of measuring a structural change in a protein when the protein is contacted with a compound, comprising the steps of:

(a) selecting a domain in the protein using an input device;

(b) providing information on an orientation of the domain when the protein is not in contact with the compound;

(c) providing information on an orientation of the domain when the protein is in contact with the compound, by:

(i) providing known atomic coordinates for the domain,

(ii) providing axial variations of NMR signals, which are generated from the protein in contact with the compound in the presence of a liquid crystalline material by two-dimensional TROSY NMR spectroscopy and depend on an orientation angle of the protein and compound in a magnetic field,

(iii) determining Saupe order matrix elements for the domain from the atomic coordinates for the domain and the axial variations of NMR signals using a computer processor, and

(iv) diagonalizing the Saupe order matrix elements to produce information on an orientation of the domain using the processor; and

(d) measuring the structural change in the protein using the processor by a difference between the information on an orientation provided in step (b) and the information on an orientation provided in step (c),

wherein a structural change in the protein when the protein and the compound are contacted is digitized as degree of orientational change by:

(v) providing directions of orientation tensor axes by a first three unit vectors perpendicular to each other, by using the information on an orientation of

the domain in the protein before the protein is contacted with the compound,
wherein the first three unit vectors are expressed by

$$\overrightarrow{e_{fx}}, \overrightarrow{e_{fy}}, \overrightarrow{e_{fz}}$$

(vi) providing directions of orientation tensor axes by a second three unit vectors perpendicular to each other, by using the information on an orientation of the domain in the protein after the protein is contacted with the compound,
wherein the second three unit vectors are expressed by

$$\overrightarrow{e_{bx}}, \overrightarrow{e_{by}}, \overrightarrow{e_{bz}}$$

(vii) denoting respective angles between the individual first unit vectors and the individual second unit vectors by a, b and c, and

(viii) giving a degree of orientational change by the following equation:
degree of orientational change = $a^2 + b^2 + c^2$.

73. (Currently Amended) The method of measurement according to claim 72, wherein the step (b) is a step of:

(b) providing information on an orientation of the domain when the protein is not in contact with the compound, by:

(v) (ix) providing known atomic coordinates for the domain,

(vi) (x) providing axial variations of NMR signals, which are generated from the protein in no contact with the compound in the presence of the liquid crystalline material by two-dimensional TROSY NMR spectroscopy and depend on the orientation angle of the protein and compound in the magnetic field,

(vii) (xi) determining Saupe order matrix elements for the domain from the atomic coordinates for the domain and the axial variations of NMR signals using the processor, and

(viii) (xii) diagonalizing the determined matrix to produce the information on an orientation of the domain.

74. (Previously Presented) The method of measurement according to claim 72, wherein the step (b) is a step of

(b) providing the information on an orientation of the domain from the atomic coordinates provided previously when the protein was not in contact with the compound.

75. (Previously Presented) The method of measurement according to claim 72, wherein in the step (c), the axial variations of NMR signals, which are generated by two-dimensional TROSY NMR spectroscopy and depend on the orientation angle of the molecules in the magnetic field, are variations along a ^{15}N axis.

76. (Previously Presented) The method of measurement according to claim 75, wherein the Saupe order matrix elements in (iii) are determined by:

with respect to a kth pair of ^{15}N nuclear spins in the domain,

providing ϕ_i^k as a vector angle of an N-H bond having the kth pair of spins in the domain to an ith molecular axis,

providing ϕ_j^k as a vector angle of an N-H bond having the kth pair of spins in the domain to a jth molecular axis,

setting a static dipolar coupling D_{nh}^0 at 23.0 kHz for a length of the N-H bond of 1.02 Å, or setting a static dipolar coupling D_{nh}^0 at 21.7 kHz for a length of the N-H bond of 1.04 Å,

determining as δ_{ij} a tensor value for chemical shift anisotropy of a ^{15}N nucleus in an arbitrary residue of the protein using the processor, and

determining the Saupe order matrix elements S_{ij} defining the molecular orientation with respect to the magnetic field using the processor, by contacting the protein with the compound in the presence of the liquid crystalline material, providing $\Delta\delta\text{trosy}(k)$ for the kth pair of ^{15}N nuclear spins of the protein by two-dimensional TROSY NMR spectroscopy, and using the $\Delta\delta\text{trosy}(k)$ together with the following equation (1):

$$\Delta\delta\text{trosy}(k) = \sum S_{ij} \{ 0.5 D_{nh}^0 \cos\phi_i^k \cos\phi_j^k + (2/3) \delta_{ij} \} \quad (1)$$

$i, j = x, y, z.$

77. (Previously Presented) The method of measurement according to claim 73, wherein in the step (b), the axial variations of NMR signals, which are generated by two-dimensional TROSY NMR spectroscopy and depend on the orientation angle of the molecules in the magnetic field, are variations along a ^{15}N axis.

78. (Previously Presented) The method of measurement according to claim 77, wherein the Saupe order matrix elements in (vii) are determined by:

with respect to a kth pair of ^{15}N nuclear spins in the domain,

providing ϕ_i^k as a vector angle of an N-H bond having the kth pair of spins in the domain to an ith molecular axis,

providing ϕ_j^k as a vector angle of an N-H bond having the kth pair of spins in the domain to a jth molecular axis,

setting a static dipolar coupling D_{nh}^0 at 23.0 kHz for a length of the N-H bond of 1.02 Å, or setting a static dipolar coupling D_{nh}^0 at 21.7 kHz for a length of the N-H bond of 1.04 Å,

determining as δ_{ij} a tensor value for chemical shift anisotropy of a ^{15}N nucleus in an arbitrary residue of the protein, and

determining the Saupe order matrix elements S_{ij} defining the molecular orientation with respect to the magnetic field, by making no contact of the protein with the compound in the presence of the liquid crystalline material, providing $\Delta\delta_{\text{TROSY}}(k)$ for the kth pair of ^{15}N nuclear spins by two-dimensional TROSY NMR spectroscopy, and using the $\Delta\delta_{\text{TROSY}}(k)$ together with the following equation (1):

$$\Delta\delta_{\text{TROSY}}(k) = \sum S_{ij} \{ 0.5 D_{nh}^0 \cos\phi_i^k \cos\phi_j^k + (2/3) \delta_{ij} \} \quad (1)$$

$i, j = x, y, z.$

79. (Cancelled)

80. (Previously Presented) The method according to claim 73, further comprising a step of identifying a position on the protein to which the compound is bound.

81. (Previously Presented) The method according to claim 80, wherein the step of identifying a position on the protein to which the compound is bound is carried out by comparing a two-dimensional TROSY NMR spectrum which comprise the information provided in the step (b) with a two-dimensional TROSY NMR spectrum which comprises the information provided in the step (c) to detect a spectral change, and identifying an amino acid residue in the protein which has induced the spectral change.

82. (Previously Presented) The method according to claim 72, wherein the liquid crystalline material comprises a mixture selected from the group consisting of:

- a mixture of dimyristoylphosphatidylcholine (DMPC) and dihexanoylphosphatidylcholine (DHPC),
- a mixture of dimyristoylphosphatidylcholine (DMPC), dihexanoylphosphatidylcholine (DHPC), and sodium dodecyl sulfate (SDS),
- a mixture of dimyristoylphosphatidylcholine (DMPC), dihexanoylphosphatidylcholine (DHPC), and cetyltrimethylammonium bromide (CTAB),
- a mixture of 1,2-di-O-dodecyl-sn-glycero-3-phosphocholine(DIODPC) and 3-(cholamidepropyl)-dimethylammonio-2-hydroxy-1-propane sulfate (CHAPS),
- a mixture of n-alkyl-poly(ethyleneglycol)/n-alkylalcohol,
- filamentous phage,
- a mixture of cetylpyridinium chloride(CPCL)-hexanol-NaCl,
- a mixture of cetylpyridinium bromide(CPBr)-hexanol-NaCl,
- a purple membrane fragment of Halobacterium species,
- microcrystalline cellulose, and
- polyacrylamide gel.

83. (Previously Presented) The method according to claim 82, wherein the liquid crystalline material is the mixture of 7.5%(w/v) composed of dimyristoylphosphatidylcholine (DMPC), dihexanoylphosphatidylcholine (DHPC), and cetyltrimethylammonium bromide (CTAB).

84-110. (Cancelled)